Remarks

Claims 1-6, 10-11, and 14-41 are pending in the present application. Claims 24-41 stand withdrawn. Claims 7-9, 12, and 13 were previously canceled. Claim 1 is amended in this paper. Claims 1-6, 10, 11, and 14-23 remain under examination.

In light of the claim amendments presented above, the additional factual evidence presented in the concurrently submitted § 1.132 declaration of Dr. Nicholas Abbott and the associated exhibits, the concurrently submitted Request for Continued Examination, and the remarks presented below, Applicants respectfully request that the Office reconsider the final rejections of claims 1-6, 10, 11, and 14-23.

CLAIM REJECTIONS – 35 U.S.C. §112, SECOND PARAGRAPH

The Office has rejected claims 1-6, 10-11, 15-20, and 22-23 under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Office has referenced the language in claim 1, step (c), "detecting the presence of the ligand on the detection surface by contacting the detection surface with liquid crystal, wherein the presence of the ligand on the detection surface is detected *by a change in the orientation of the liquid crystal* contacted with the detection surface." The Office alleges that it unclear as to how a "change in orientation" would be assessed.

In reviewing a claim for compliance with 35 U.S.C. §112, second paragraph, the Examiner must consider the claims as a whole to determine whether the claim apprises the skilled artisan of its scope, and therefore serves the required notice function by providing clear warning to others as to what constitutes infringement of the claim. MPEP 2173.02, citing *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379 (Fed. Cir. 2000). Definiteness of claim language is to be analyzed, not in a vacuum, but in light of the content of the disclosure and the teachings of the prior art. MPEP 2173.02. The proper test is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir 1986). If one skilled in the art is able to ascertain the meaning of the claim in light of the specification, 35 U.S.C. §112, second paragraph, is satisfied. *Id.*

In making this rejection, the Office did not consider the meaning of the rejected claims in light of the specification. In light of the specification, "change in orientation" means that the orientation of the liquid crystal in contact with the detection surface varies between areas of the detection surface containing bound ligand and areas of the detection surface that do not contain bound ligand.

Paragraph [0055] of the specification explains that a disordering or disruption of the liquid crystal on a detector surface (i.e. inconsistent orientation of the liquid crystal in contact with the detection surface) indicates the presence of the ligand on the detector surface. This is further clarified in Figure 1.1, which illustrates in general how the claimed method works. On the bottom of the figure is a drawing showing the change in orientation of the liquid crystal. The drawing shows that the recited change in orientation is a change in the orientation of the liquid crystal in contact with regions of the detection surface containing the bound ligand relative to the orientation of liquid crystal in contact with regions of with the same detection surface that do not contain the bound ligand.

Further, Figure 13 (explained in paragraph [0208]) shows liquid crystal alignment in both a stamped (WT) and control (parental) situation. As shown in the twelve hour results and explained further in paragraph [0208], the printed samples showed disruption *in the printed regions* (as compared to the non-printed regions, emphasis added), while the control samples did not. It is this difference in orientation between the liquids crystal in contact with the printed regions of a detection surface as compared to the orientation of the liquid crystal in contact with the non-printed regions of the same surface that allows for the optical detection of the ligands in the printed regions by visual contrasts in the optical image. See optical image at upper right in Fig. 13. No such contrast and detection is present in the control surface. See optical image at lower right in Fig. 13.

Thus, when viewed in light of the specification, it is clear that the recited change in the orientation of the liquid crystal are the changes that occur at the regions of the detection surface containing bound ligand relative to the liquid crystal orientation at other regions of the detection surface where ligand is not present. Because the meaning of the rejected claims is clear when properly considered in light of the specification, Applicants respectfully ask the Office to

reconsider and reverse these rejections, in accordance with the January 21, 2010 decision of the Board of Patent Appeals and Interferences.

CLAIMS REJECTIONS – 35 U.S.C. §103

The Office has rejected claims 1-6, 10-11, 15-20 and 22-23 as being unpatentably obvious over Bernard et al. or, alternatively, Renault et al. in view of Abbott et al. Specifically, the Office alleges that Bernard et al. teach a method of detecting a ligand comprising the step of (a) contacting a sample having a ligand (e.g., ^{125}I-IgG) with an affinity substrate (PDMS stamp) wherein the affinity substrate comprises an array of receptors that are capable of specifically binding the ligand. The Office further alleges that Bernard et al. teach a step (b) of contacting the affinity substrate with a detection surface (glass or polystyrene) wherein a portion of the ligand that is bound by the receptor is transferred to the detection surface. The Office acknowledges that Bernard et al. do not teach detection of the ligand on the detection surface by liquid crystal but, instead, utilize radioactive or fluorescent labels attached to the target ligands.

In similar fashion, the Office alleges that Renault et al. teach a method of detecting a ligand (e.g., an antibody) by contacting a ligand-containing sample with an affinity substrate (PDMS stamp), followed by transfer of the ligand to a detection surface where detection of the ligand is accomplished by fluorescent or gold-labeled antibodies via fluorescence microscopy or atomic force microscopy. A with Bernard et al., the Office acknowledges that Renault et al. fail to teach detection of the ligand via liquid crystal techniques.

The Office alleges that Abbott et al. teach a device having a detection surface to which a ligand may be transferred and its presence subsequently detected by using a liquid crystal. The Office states one of skill would have been motivated to combine the teachings of Bernard et al. and Abbott et al. or, alternatively, Renault et al. and Abbott et al., because Abbott et al. teach that liquid crystal detection surfaces do not require pre-labeling of the ligand and, as such, one would be motivated to stamp the affinity-captured ligand onto the device of Abbott et al. in order to avoid the need for fluorescent or other labels of the ligands. The Office further states that "one would have a reasonable expectation of success in affinity stamping the surface of Abbott et al. according to the methods of Bernard et al. or Renault et al. because the surface of Abbott et al. is compatible with microcontact printing."

In response, without agreeing to the Office's rejections and solely to move prosecution forward, Applicants have amended claim 1 to explicitly recite the characteristics of the detection surface used in the present invention that (1) are central to the success of the method, and (2) clearly distinguish the detection surface used in the present method from the detection surfaces taught by Bernard et al., Renault et al , and Abbott et al. Specifically, claim 1 as currently amended recites that the detection surface used is capable of both "uniformly anchoring liquid crystal in the absence of the ligand" and "binding non-specifically to the ligand." All the other rejected claims depend from claim 1, and thus recite the same limitations. None of the detection surfaces taught by Bernard et al., Renault et al., or Abbott et al. have both of these characteristics.

Support for this amendment is found in the as-filed application. As to the detection surface being capable of uniformly anchoring liquid crystal, see paragraph [0091] of the as-filed specification (paragraph [0085] of the published application). As to the detection surface being capable of non-specifically binding to the ligand, see paragraph [0065] of the as-filed specification (paragraph [0059] of the published application).

To provide further factual evidence showing (1) the importance of these two features of the detection surface to the presently claimed method, (2) that the methods disclosed by the cited documents do not use a detection surface having these two features, and (3) the technical difficulties encountered by the inventors in developing detection surfaces that could be used successfully with the present method, Applicants are submitting with this response for the Office's consideration the § 1.132 Declaration of Dr. Nicholas Abbott, the first named inventor of both this application and Abbott et al.

In his Declaration, Dr. Abbott first explains that the key to the success of the presently claimed method was to develop detection surfaces having two essential characteristics: that the detection surfaces be capable of non-specifically capturing analyte from a stamp, and that the detection surface anchor liquid crystal in such a way that a detectable change in liquid crystal orientation occurs when the analyte is captured. The detection surfaces taught in the cited documents do not have both of these properties (see Declaration, paragraphs 5-6).

In particular, the bare glass or polystyrene detection surfaces taught by Bernard/Renault do not uniformly (homeotropically) anchor liquid crystal. Instead, liquid crystal on such surfaces

generally exhibit a random planar orientation (see Declaration, paragraph 7). As further evidence of the planar orientation of liquid crystal in direct contact with an untreated glass or polystyrene surface, Dr. Abbott cites four non-patent documents that are included with this filing as exhibits to the Declaration (see Declaration, paragraph 7).

Cognard (Exhibit A) teaches that the alignment of liquid crystal on glass surfaces, such as those taught by Bernard/Renault, has poor reproducibility and uniformity, because "the substrate surface is ill defined." Although some variations in alignment have been reported, depending glass surface treatment, Cognard reports that the vast majority of glass treatments lead to parallel alignment of liquid crystal (see Cognard, page 6). Similarly, Janning (Exhibit B) reports that liquid crystal orientation on a substrate requires the deposition of an orienting layer on clean glass plates; a glass surface alone will not orient liquid crystal (see Janning, page 173).

Kang et al. address the orientation of liquid crystal on a polystyrene surface, the other surface type taught by Bernard/Renault. Kang et al. report that random planar liquid crystal alignment was observed for liquid crystal cells made from untreated polystyrene (see Kang et al., pages 930-931). Similarly, Hyo et al. (Exhibit D) report that random planar liquid crystal alignment was observed for liquid crystal cells fabricated using untreated polystyrene (see Hyo et al., page 510). Even if the polystyrene is mechanically rubbed, the resulting anchoring energy of the surface is too low to provide a useful liquid crystal device, and in any case, any homogeneous liquid crystal anchoring gained by rubbing is lost after a day (see Hyo et al., page 506). These newly presented exhibits provide further evidence that the glass or polystyrene surfaces appropriate for affinity microcontact printing, as taught by Bernard/Renault, simply would not work for liquid-crystal based detection.

In addition, Dr. Abbott's lab has confirmed that glass and polystyrene surfaces show identical liquid crystal orientation (planar orientation) both with and without the presence of analyte on the surface (see Declaration, paragraphs 7-8). So the detection surface taught by Bernard/Renault could not be used with the present method (see Declaration, paragraphs 7-8).

The newly submitted evidence shows that (1) the skilled artisan at the time of the invention would not have had a reasonable expectation of success in combining the teachings of the cited documents to practice the claimed method using the detection surface recited in claim 1 as amended, (2) the skilled artisan at the time of the invention would not have had a motivation

to combine the teachings of the cited documents to practice the claimed method using the detection surface recited in claim 1 as amended, and (3) the inventors overcame significant technical hurdles to develop a working detection surface for use in the claimed method.

1. No reasonable expectation of success in practicing the claimed method

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success in making the proposed modification. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). An obviousness rejection may be supported if all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1395 (2007). Here, there is no such finding that stands up to the newly presented evidence contained in Dr. Abbott's Declaration.

The successful detection of an affinity stamped ligand on a detection surface using the change in orientation of liquid crystal, as opposed to ligand detection by fluorescent or radioactive labeling as taught by Bernard/Renault, is not a mere substitution of one known element for another to obtain predictable results. The development of detection surfaces that can both uniformly anchor liquid crystal to facilitate liquid crystal-based detection and capture analyte from a stamp was essential to the present invention. Although the bare glass or polystyrene detection surfaces taught by Bernard/Renault can non-specifically capture analyte from a stamp, these surfaces do not uniformly anchor liquid crystal in a way that would facilitate liquid crystal-based detection. Furthermore, if the detection surfaces taught by Bernard/Renault are coated or otherwise modified to facilitate detection of analyte by changes in liquid crystal orientation, then the surfaces will no longer predictably capture analyte from a stamp.

For example, Dr. Abbott's lab found that the detection surfaces taught by Abbott et al., which, unlike the detection surfaces taught by Bernard/Renault, facilitate liquid crystal-based analyte detection, will not also capture analyte from a stamp (see Declaration, paragraph 11). Because the Office's asserted findings of a reasonable expectation of success in combining the teachings of the cited documents do not address this fundamental problem (see Declaration,

paragraphs 9-10), they are not sufficient to establish the required reasonable expectation of success. At the time of the invention, the skilled artisan would not have had a reasonable expectation of success in using the teachings of the cited documents to practice the claimed method.

2. No motivation to make the proposed substitution

In making an obviousness rejection, the Office may base its rationale on some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to the artisan to combine the references. MPEP 2143(G). If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Here, because the Office's proposed modification would render the method of Bernard/Renault unsatisfactory for its intended purpose, there is no motivation to make the proposed modification. The method taught by Bernard/Renault uses affinity microcontact printing to transfer a labeled analyte to a glass or polystyrene detection surface. The analyte is then detected by pinpointing signals from the radioactive or fluorescent labels.

The Office proposes that the methods of Bernard/Renault be modified so that liquid crystal-based detection could be used to detect the analyte, as in the claimed invention. As discussed previous and in the Abbott Declaration, this would require modifying the detection surface taught by Bernard/Renault so that it would no longer predictably accept analyte using affinity microcontact printing. Thus, the modified method would longer predictably work for its intended purpose, and there is no sufficient motivation to make the proposed modification.

3. Difficulties encountered in making the proposed modification

Additional evidence of the difficulties the inventors overcame to develop the detection surfaces that work in the claimed invention further counter the Office's assertion that liquid-crystal based detection could be predictably and easily applied to the methods taught by Bernard/Renault. Specifically, the inventors found that the detection surfaces taught by Abbott et al. would not work with the claimed method, and spent substantial time and money in developing working detection surfaces (see Declaration, paragraphs 11-12). Thus, Applicants'

own experience shows that the claimed method, particularly the development of a working detection surface, was difficult and unpredictable, rather than predictable and obvious.

In sum, because (1) the skilled artisan at the time of the invention would not have had a reasonable expectation of success in modifying the teachings of the cited documents to practice the claimed method, (2) there would have been no motivation to modify the teachings of the cited documents to practice the claimed method, and (3) the inventors own experience shows that the Office's proposed modification would not have been predictable or obvious, Applicants respectfully request that the Office reconsider and reverse the obviousness rejections over either Bernard et al. or Renault et al. in view of Abbott et al.

Other Obviousness Rejections

The Office has rejected Claim 14 as being unpatentably obvious over Bernard et al. or Renault et al. in view of Abbott et al, and further in view of Tang et al. (U.S. Patent 5,886,195). Tang et al. allegedly teach anti-phosphotyrosine antibodies, which may be used to measure autophosphorylation of EGFR and thereby an increase in EGF activity. The Office asserts that it would have been obvious to the artisan to employ the anti-phosphotyrosine antibodies taught by Tang et al. as the receptor molecules on the affinity substrate in a method for detecting a ligand based on Bernard et al. and Abbott et al. or, alternatively, Renault et al. and Abbott et al.

Claim 21 stands rejected as being unpatentably obvious over Bernard et al. or Renault et al. in view of Abbott et al, and further in view of Choi et al. (U.S. Patent 6,292,296). Choi et al. allegedly teach photo-alignment in liquid crystal devices. The Office asserts that it would have been obvious to the artisan to employ the photo-alignment with ultraviolet light as taught by Choi et al. in order to align the liquid crystal detection surface while avoiding the known disadvantages of other methods.

As with all the other rejected claims, both claims 14 and 21 depend from base claim 1. Because claim 1 as amended is not obvious over Bernard/Renault in view of Abbott et al., and because neither Tang et al. nor Choi et al. cure the deficiencies noted in the obviousness rejections over Bernard/Renault in view of Abbott et al., claims 14 and 21 are not obvious. Applicants respectfully request that the Office reconsider and reverse these obviousness rejections.

PROVISIONAL DOUBLE PATENTING REJECTIONS

The Office has provisionally rejected claims 1-6, 10-11, and 14-23 as being unpatentable on the grounds of nonstatutory obviousness-type double patenting over claims 18-23 of co-pending Application No. 11/542,432 in view of Renault et al. The Office has also provisionally rejected claims 1-6, 10-11, and 14-23 as being unpatentable on the grounds of nonstatutory obviousness-type double patenting over claims 21-34 of co-pending Application No. 11/418,755 in view of Renault et al.

Application No. 11/418,755 was abandoned on April 13, 2009 and is no longer co-pending. Thus, the provisional rejection based on this application is moot.

As to the remaining provisional nonstatutory obviousness-type double patenting rejection, the present application was filed earlier than co-pending Application No. 11/542,432. If a provisional obviousness-type double patenting rejection is the only rejection remaining in the earlier-filed of two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection without requiring a terminal disclaimer. MPEP 804(1)(B)(1). Accordingly, Applicants respectfully request that the Office withdraw this remaining rejection.

CONCLUSION/FEES

In view of the present claim amendments, the concurrently submitted Abbott Declaration and associated exhibits, and the remarks presented herein, Applicants respectfully request that claims 1-6, 10, 11, 14-23 be allowed. The Examiner is urged to telephone the undersigned in the event a telephone discussion would be helpful in advancing the prosecution of this case.

In order for this response to be considered, it is accompanied by a Request for Continued Examination. Please charge the small entity RCE fee to Deposit Account 17-0055.

No other fees are believed due at this time. However, the Office is authorized to charge any extension fee, or any other surcharges or underpayment associated with this filing, as deemed necessary and appropriate, to Deposit Account 17-0055.

Respectfully submitted,

Nick Abbott, et al.

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